REMARKS

I. Status of Claims.

Claims 1-13 are pending.

Claims 2 and 6 are amended in a manner that is believed to overcome rejections contained in the pending Office Action. The amendments to the claims have been made solely for reasons of clarity. Support for these amendments can be found throughout the drawings, specification and claims as originally filed. No new matter or issues are believed to be introduced by these amendments.

IV. Rejection of claims 1, 3-6, 9 and 11-12 under 35 USC 112, first paragraph.

In the Office Action dated March 3, 2004, the Examiner rejected claims 1, 3-6, 9 and 11-12 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner stated that the rejected claims are drawn to a method for modulating behavioral and neurological adaptive responsiveness to stress by applying to the central nervous system a therapeutically effective amount of an inhibitor of the DP VI enzyme. The Examiner stated that the "instant specification fails to define any specific criteria, which clearly identify behavioral and neurological adaptive responsiveness to stress one would wish to modulate. Applicants strongly oppose this position and respectfully traverse this rejection.

Applicants have provided multiple examples that contain specific criteria of behavioral and neurological adaptive responsiveness to dosing within various animals studies the results of which can be extrapolated for use in humans by those skilled in the art without undue experimentation. Applicants would respectfully direct Examiner's attention to the extensive specific criteria within Examples 1-4 that more than fully comply with the requirements of 35 USC 112, first paragraph. The criteria measured for dose response are also the criteria to be modulated. Applicants specifically direct Examiner's attention to the standard methodology used within Examples 1-4 to assess stress induced treatment response. With reference to the Examples it is noted that there are presented three standardized tests that measure behavioral and neurological adaptive responsiveness to stress which one might wish to modulate including a

social interaction test, a stress induced body weight loss test and an anxiety in the social interaction test. The utility of a chemical compound for a particular disease state may be confirmed by establishing that it possesses properties of therapeutic value through the aforementioned tests conducted on standard experimental animals. Applicants have disclosed numerous examples and data on standardized laboratory animals, which can clearly be used by one skilled in the art to understand therapeutic utility. No undue experimentation is required to confirm the possession of such therapeutic effectiveness.

Applicants' situation is unlike that of Ex parte Stevens, 16 U.S.P.Q.2d 1379, 1380. In that case the applicant had **no** evidence whatsoever, either *in vivo* or *in vitro*, to support the alleged utility of treating cancer. Rather, in the present application there is ample evidence of treatment utility based upon the animal test results summarized in the four examples. These examples, using standardized tests upon experimental animals, provide a reasonable indication to one skilled in the art that the present invention would in fact have its asserted utility in Applicants' claimed method for the treatment of "the psychophysiological effects of stress".

Applicants would also like to point out that the Patent and Trademark Office has the burden of showing that the disclosure entails undue experimentation. In Re Angstadt (CCPA 1976) 537 F2d 498, 190 USPQ 214., It is respectfully submitted that the Patent Office has not carried this burden or provided the required reasonable basis for contending that one skilled in the art would not be able to practice the invention as claimed. Gould v. Mossinghoff 229 U.S.P.Q. 1, 13 (D.C. D.C. 1985). Accordingly, Applicants respectfully submit that any experimentation which might be required would not rise to the level of undue experimentation.

As to Claim 1, there is no basis for the Examiner's opinion of lack of enablement, as is required to maintain such a rejection. Gould v. Mossinghoff, 229 U.S.P.Q. 1, 13-14 (D.D.C. 1985) aff'd in part, vacate in part, and remanded *sub nom*, Gould v. Quigg, 3 U.S.P.Q. 2d 1302 (Fed. Cir. 1987)("In examining a patent application, the P.T.O. is required to assume that the specification complies with the enablement provision of section 112 unless it has 'acceptable evidence or reasoning' to suggest otherwise"; the burden of persuasion is on the P.T.O.); In re Armbruster, 185 U.S.P.O. 152 (C.C.P.A. 1975).

The Examiner references neither the level of knowledge of "one of ordinary skill in the art," nor the nature of the impediments to enablement one might encounter. The Examiner is respectfully requested to provide an affidavit under §104(d)(2) as to the reasoning under which enablement is questioned.

In the alternative, Applicants respectfully request that this rejection be withdrawn.

V. Rejection of Claims 1-13 under 35 USC 112, second paragraph.

The Examiner rejected claims 1-13 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of Applicants' invention.

A. DPIV-Like Enzyme: Claims 1 and 2 were rejected under 35 USC 112, second paragraph for the term "DP IV –like" enzyme. The Examiner stated that it was not obvious, which enzymes are to be included or excluded by the limitation "like." Applicants respectfully traverse this rejection.

Claims 1 and 2 are directed to "DP IV and DP IV-like enzymes." It is respectfully submitted that one skilled in the art would, from simply reading the claim, clearly understand that the 'like' enzymes would be those enzymes having identical or similar enzymatic activity as that of the dipeptidyl peptidase IV enzyme. But one skilled in the art has substantially more guidance than just the claims. More particularly, the Examiner's attention is drawn to page 20 lines 27-35 discussing DP-IV "like" enzyme activity. It is clear from the instant specification that DP-IV "like" enzyme activity is understood to mean where such inhibition will result in a reduction or delay in the decrease of the concentration of functionally active NPY (1-36). Applicants further draw the Examiner's attention to page 10 lines 24-29 of the instant application where the suffix 'like' is used in the context of anxiolytic like effects. From this context it is understandable that "like" means generally the same as. Similarly, the Examiner's attention is drawn to page 12 lines 25-29 where anti-epileptic "like" drugs are discussed; and to page 12 line 35 continuing to page 13 line 8 and lines 19-24 addressing NPY "like" –immunoreactivity. The Examiner's attention is further drawn to the dictionary meaning of "like" which is defined as

"having the characteristics of; similar to or typical of" (Webster's Ninth New Collegiate Dictionary 1988). It is clear from these passages and the conventional dictionary meaning, that one skilled in the art would accept these as commonly used terms and would understand the metes and bound of Applicants' invention. Applicants therefore respectfully request that this rejection may be properly withdrawn.

B. Other Substrate Sharing Properties: Further rejection was made to claim 2 for the recitation of "other substrates sharing similar properties." The Examiner stated that it was not clear what "other substrates" were intended by the claim. Applicants have amended claim 2 to clearly define their invention. Applicants respectfully submit that this rejection has now been overcome.

C. Antecedent Basis: Rejection was made to claim 6 as the limitation DP IV inhibitors in claim 1. Applicants have amended claim 6 and respectfully submit that this rejection has now been overcome.

D. Indefinite Claims: The Examiner rejected claims 3-5, 7-13 as being indefinite for being dependent from indefinite claims. Applicants have amended claim 2 as noted above and have traversed the 35 USC 112, second paragraph rejection as set forth above and therefore respectfully submit that these rejections have been overcome as well.

VI. Rejection of claims 2, 7-8, 10 and 13 under 35 USC 102(b).

The Examiner rejected claims 2, 7-8, 10 and 13 under 35 USC 102(b) as being anticipated by Powers et al. (WO 95/2961, 1995, Document BL, IDS of Paper No. 2) ("Powers"). Applicants respectfully traverse this rejection.

A. Examiner's Rejection: The Examiner' rejection stated that Powers discloses administration of inhibitors of dipeptidyl peptidase IV and such administration leads to the decrease of enzymatic activity of DPIV and consequently to reduction of degradation of its natural endogenous substrate. The Examiner further stated that claim 2 and its dependant claims

7-8, 10 and 13 are directed to a method for reducing degradation of NPY and not to the treatment of "psychophysiological effects of stress".

B. Applicants' Claimed Invention: Applicants' claimed invention as described in amended claim 2, from which all subsequent claims depend, is directed to the "treatment of psychophysiological effects of stress" resulting from central nervous system disorders such as anxiety. Applicants claimed method of treating central nervous system disorders such as anxiety is by the administration of DP-IV inhibitors.

C. Disclosure of Powers: Power discloses the use of peptidyl derivative of diesters of α-aminoalkylphosphonic acids, particularly those with proline or related structures, their use in inhibiting serine proteases with chymotrypsin-like, elastase-like, and dipeptidyl peptidase IV specificity. The disclosure of Powers is directed to the use of DPIV inhibitors as anti-inflammatory agents, anticoagulants, anti-tumor agents, and anti-AIDS agents.

D. Deficiencies of Powers: Claim 2 as amended, from which all rejected claims depend, is directed to the "treatment of psychophysiological effects of stress" resulting from central nervous system disorders such as anxiety. Unlike Applicants' claimed invention, Powers is completely devoid of any disclosure of the use of DP-IV inhibitors for the treatment of central nervous system disorders and specifically any teaching of "applying to the central nervous system" a therapeutically amount of DP-IV inhibitors. Given the amendment to claim 2 and the absence of an anticipatory teaching in Powers, Applicants respectfully request that this rejection be withdrawn.

VII Rejection of claims 1, 3-6, 9 and 11-12 under 35 USC 102(b).

The Examiner rejected claims 1-13 under 35 USC 102(b) as being anticipated by Powers et al. (WO 95/2961, 1995, Document BL, IDS of Paper No. 2) (Power).

A. Examiner's Rejection: The Examiner's rejection stated that Powers discloses inhibitors of dipeptidyl peptidase IV and their use of administration as anti-inflammatory agents, anticoagulants, anti-tumor agents and anti-AIDS agents. Administration of a therapeutic amount of inhibitors of Powers leads to the decrease of enzymatic activity of DPIV and consequently to

the reduction of degradation of its natural endogenous substrate. As such, the administration of DPIV inhibitors as disclosed by Powers leads to reduction in stress responsiveness and anxiety.

B. Applicants' Claimed Invention: Applicants' claimed invention as set forth in claim 1, and claim 2 from which the other cited claims depend, is directed to the "treatment of psychophysiological effects of stress" resulting from central nervous system disorders such as anxiety. Applicants' claimed invention is directed to the beneficial neurological and psychophysiological effects that result from the inhibition of DPIV-like enzymatic activity within the central nervous system by "applying to the central nervous system a therapeutically effective amount of an inhibitor of dipeptidyl peptidase."

C. Disclosure of Powers: Power discloses the use of peptidyl derivative of diesters of α-aminoalkylphosphonic acids, particularly those with proline or related structures, their use in inhibiting serine proteases with chymotrypsin-like, elastase-like, and dipeptidyl peptidase IV specificity and their roles as anti-inflammatory agents, anticoagulants, anti-tumor agents, and anti-AIDS agents.

F. Deficiencies of Cited References: Unlike Applicants' claimed invention, Powers does not disclose the "treatment of psychophysiological effects of stress" resulting from central nervous system disorders such as anxiety using an inhibitor of DP IV. Powers also does not disclose the treatment of stress by "applying to the central nervous system a therapeutically effective amount of an inhibitor of dipeptidyl peptidase." It is made clear throughout the description of the present invention that the therapeutic targets of the present invention are the receptors of neuropeptides. The main target is the neuropeptide Y receptor Y1. These receptors are localized in the central nervous system (brain) of mammals. As it is known in the art, the central nervous system is a separate compartment of the body/organism of mammals, which is strongly demarcated from the rest of the body by the so called "blood-brain-barrier." Accordingly, the claims of the present invention specify inhibition of dipeptidyl peptidase IV (DP IV) activity by "applying to the central nervous system a therapeutically effective amount of an inhibitor of dipeptidyl peptidase" in order to reach the desired pharmaceutical target.

As has been clearly enunciated by the Federal Circuit: Anticipation requires the presence in a single prior art reference the disclosure of each and every element of the claimed invention, arranged as in the claim. Lindermann Maschinenfabrik GMBH v. American Hoist and Derrick

Co., 221 USPQ 481, 485 (Fed Cir. 1984) (emphasis added). Here the requirement of showing each and every element of Applicant's claimed invention in a single prior art reference has not been met since Powers fails to disclose Applicants' claimed invention as detailed above. In light of the above, it is respectfully submitted that the 35 U.S.C. §102(b) is improper, may be properly withdrawn, and Applicants so request.

VII. Rejection of claims 1-13 under 35 USC 102(e).

The Examiner rejected claims 1-13 under 35 USC 102(e) as being anticipated by Demuth et al., U.S. Patent No. 6,319,893 (Demuth '893). Applicants respectfully traverse this rejection.

A. Examiner's Rejection: The Examiner stated that Demuth '893 describes the administration to a mammal of therapeutically effective amounts of an inhibitor of DPIV. The Examiner further stated that Demuth '893 also discloses methods of administration (parenterally, orally), pure forms of inhibitors, and formulations with physiologically acceptable adjuvants.

B. Applicants' Claimed Invention: Applicants' claimed invention as set forth in the claims is directed to the "treatment of psychophysiological effects of stress" resulting from central nervous system disorders such as anxiety. The instant claims are directed to methods of treating these central nervous system disorders such as anxiety through the administration of DP-IV inhibitors by "applying to the central nervous system a therapeutically effective amount of an inhibitor of dipeptidyl peptidase".

C. Disclosure of Demuth '893: Demuth '893 discloses a method of raising the blood sugar level in a mammal having hypoglycemia. The method disclosed in Demuth '893 reduces degradation of glucagons by administering to the mammal a therapeutically effective amount of an inhibitor of dipeptidyl peptidase IV and physiologically acceptable adjuvants and/or excipients.

D. Deficiencies of Demuth '893: Demuth '893 is completely devoid of any disclosure related to DP-IV inhibitors for the treatment of central nervous system disorders through the use

of DP IV inhibitors by "applying to the central nervous system a therapeutically effective amount of an inhibitor of dipeptidyl peptidase." Applicants respectfully request that this rejection be withdrawn.

VIII. Rejection of claims 1-13 under Obviousness-type Double Patenting.

A rejection was made to claims 1-13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,319,893 (Demuth '893). Applicants respectfully but vigorously suggest that the claimed subject matter of the rejected claims differ from that of the claims of Demuth '893, as discussed immediately above, however, in the interest of moving this matter to allowance Applicants may upon notification of allowable subject matter execute a terminal disclaimer.

CONCLUSION

The claims remaining within the application are believed to patentably distinguish over the prior art and to be in condition for allowance. Early and favorable consideration of this application is respectfully requested.

Respectfully submitted,

John C. Serio, Reg. No. 39,023
Attorney(s) for Applicants
Customer No. 21710
Brown Rudnick Berlack Israels LLP
One Financial Center, Box IP
Boston, MA 02111
Tel.: 617- 856-8238
Fax: 617-856-8201
Email: ip@brbilaw.com

Dated : May 3, 2004